

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Please amend claims 4, 5 and 40 as indicated below.

Listing of Claims

1. (Previously Presented): A modified bacterial surface layer (S-layer) protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said unmodified protein is:

- (a) able to crystallize to form a crystalline monolayer;
 - (b) from a *Lactobacillus* bacterium;
 - (c) from 40 to 70 kd in size; and
 - (d) highly basic with a pI of at least 9,
- where the insertion site of said heterologous polypeptide is:
- (i) at a position from amino acids 1 to 20;
 - (ii) at a position from amino acids 35 to 55;
 - (iii) at a position from amino acids 100 to 130;
 - (iv) at a position from amino acids 110 to 140;
 - (v) at the position of amino acid 193; and/or
 - (vi) at a position from amino acids 340 to 360.

2. (Previously Presented): A protein according to claim 1 wherein the heterologous polypeptide is a functional polypeptide or a polypeptide of interest.

3. (Previously Presented): A protein according to claim 1 wherein the protein retains most of the full length sequence of the unmodified S-layer protein.

4. (Currently Amended): A protein according to claim 1 which:

- (e) has a crystallisation crystallization or N-terminal domain that is predominantly hydrophobic; or
- (f) has a C-terminal domain which is either predominantly basic or hydrophilic; or
- (g) has alternating hydrophobic and hydrophilic regions.

5. (Currently Amended): A protein according to claim 1 wherein the heterologous polypeptide is inserted at a location in the protein either so that it is:

- (h) exposed, or present on the cell surface;
- (i) present in the surface layer, or the cell wall; or
- (j) is protected from external proteolytic processing or is not recognised recognized or bound by external antibodies.

6. (Previously Presented): A protein according to claim 1 wherein the modified or unmodified protein:

- (k) crystallizes, optionally into an oblique lattice; and/or
- (l) has a cell wall anchor domain.

7. (Cancelled):

8. (Previously Presented): A protein according to claim 1 which in unmodified form is from *Lactobacillus acidophilus*, *L. crispatus*, *L. helveticus*, *L. amylovorus*, or *L. gallinarum*.

9. (Withdrawn): A fragment of a protein according to claim 1 which is:

- a) an N-terminal fragment or a fragment that is capable of forming a dimer with another such fragment or a trimer with two other such fragments;
- b) capable of forming dimers with another such fragment and either
 - (i) includes an immunodominant or exposed loop region and is from 20 to 200 amino acids long; or
 - (ii) excludes an entire immunodominant or exposed loop region and is from 20 to 155 amino acids long.

10. (Withdrawn): A polynucleotide encoding a protein according to claim 1.

11. (Withdrawn): A vector comprising a polynucleotide according to claim 10.

12. (Withdrawn): A host cell comprising, or which is has been transformed with a vector according to claim 11.

13. (Withdrawn): A bacteria expressing a surface layer (S-layer) protein according to claim 1 or a fragment thereof which is:

a) an N-terminal fragment or a fragment that is capable of forming a dimer with another such fragment or a trimer with two other such fragments;

b) capable of forming dimers with another such fragment and either

(i) includes an immunodominant or exposed loop region and is from 20 to 200 amino acids long; or

(ii) excludes an entire immunodominant loop region and is from 20 to 155 amino acids long.

14. (Withdrawn): A bacteria according to claim 13 which is a lactic acid bacteria.

15. (Withdrawn): A modified bacteria which has been modified to express a heterologous surface layer (S-layer) protein, wherein said heterologous surface layer (S-layer) protein is a modified bacterial surface layer (S-layer) protein according to claim 1.

16. (Withdrawn): A bacteria according to claim 15 which would not normally, or as a wild-type or in unmodified form does not, possess a surface layer.

17. (Withdrawn): A modified bacteria according to claim 15 which is a *Lactobacillus* cell and/or the S-layer has its own, original, cell wall anchor.

18. (Withdrawn): A bacteria according to claim 15 which is a *Lactobacillus* bacterial cell, and/or the S-layer protein is from *Lactobacillus* bacteria.

19-20. (Cancelled):

21. (Withdrawn): A modified bacteria expressing only, or homogeneously, a heterologous or modified surface layer (S-layer) protein according to claim 1.

22. (Withdrawn): A bacteria according to claim 21 having a genome which includes a polynucleotide encoding a heterologous S-layer protein, and/or where the polynucleotide

encoding the normal or wild-type S-layer protein has been silenced, replaced, switched off or otherwise rendered non-expressed.

23. (Withdrawn): A bacteria according to claim 22 wherein the modified S-layer protein is the sole or only S-layer protein expressed by the bacterial cell and/or the cell does not express any wild-type S-layer protein.

24. (Withdrawn): A bacteria according to claim 22 wherein the S-layer protein is located on the surface of the cell wall and/or a multiplicity of S-layer proteins form an S-layer.

25. (Withdrawn): A vaccine comprising a bacteria according to claim 13, a modified bacteria which has been modified to express a heterologous surface layer (S-layer) protein, wherein said heterologous surface layer (S-layer) protein is a modified bacterial surface layer (S-layer) or a modified bacteria expressing only, or homogeneously, a modified surface layer (S-layer) protein, wherein said bacteria has GRAS (generally regarded as safe) status.

26. (Withdrawn): A vaccine according to claim 25 which is an oral or nasal vaccine and/or additionally comprises an adjuvant.

27. (Withdrawn): A sheet or monolayer or 2-dimensional array comprising a plurality of bacterial surface layer proteins, at least one of which is modified protein according to claim 1.

28. (Withdrawn): A solid surface, liquid-air interface, lipid film, liposome or solution comprising a sheet, monolayer or array according to claim 27.

29. (Withdrawn): A solid surface according to claim 28 to which is bound one or more (macro) molecules, such as an enzyme, antibody or other binding molecule, receptor, antigen or ligand.

30. (Withdrawn): A solid surface comprising a layer of S-proteins, at least a plurality of which are modified proteins according to claim 1, sandwiched between the surface and a layer of functional molecules.

31. (Withdrawn): A sensor, molecular sieve or ion trap comprising a sheet, layer or array

according to claim 27 or a surface comprising a sheet, monolayer or array.

32. (Withdrawn): A sensor, molecular sieve or ion trap comprising a solid surface comprising a layer of S-proteins, at least a plurality of which are modified proteins according to claim 1, sandwiched between the surface and a layer of functional molecules.

33. (Cancelled):

34. (Previously Presented): A protein according to claim 8 wherein the modified protein is from *Lactobacillus acidophilus*.

35. (Withdrawn): A protein according to claim 34 wherein the heterologous polypeptide is inserted at a location:

- (i) from amino acid 1 to amino acid 20 of SEQ ID NO: 2;
- (ii) from amino acid 35 to amino acid 55 of SEQ ID NO: 2;
- (iii) from amino acid 100 to amino acid 130 of SEQ ID NO: 2; and/or
- (iv) from amino acid 110 to amino acid 140 of SEQ ID NO: 2.

36. (Withdrawn): A protein according to claim 35 wherein the heterologous polypeptide is inserted at a location:

- (i) from amino acid 5 to amino acid 10 of SEQ ID NO: 2;
- (ii) from amino acid 40 to amino acid 50 of SEQ ID NO: 2;
- (iii) from amino acid 110 to amino acid 120 of SEQ ID NO: 2; and/or
- (iv) from amino acid 120 to amino acid 130 of SEQ ID NO: 2.

37. (Withdrawn): A protein according to claim 36 wherein the heterologous polypeptide is inserted at position 7, 45, 114 and/or 125 of SEQ ID NO: 2.

38. (Withdrawn): A method of using a protein according to claim 1, said method comprising administering the modified protein or a bacteria expressing the modified protein to a human or animal by mucosal, basal, oral, or vaginal delivery.

39. (Withdrawn): A method of making a protein according to claim 1, said method comprising cultivating a host cell under conditions to provide for expression of the proteins and recovering the expressed protein.

40. (Currently Amended): A modified bacterial surface layer (S-layer) protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said unmodified protein is:

- (a) able to crystallize to form a crystalline monolayer;
 - (b) from a *Lactobacillus* bacterium;
 - (c) from 40 to 70 kd in size; and
 - (d) highly basic with a pI of at least 9,
- where the insertion site of said heterologous polypeptide is:
- (i) at a position from amino acids 1 to 20;
 - (ii) at a position from amino acids 35 to 55;
 - (iii) at a position from amino acids 100 to 130;
 - (iv) at a position from amino acids 110 to 140;
 - (v) at the position of amino acid 193; and/or
 - (vi) at a position ~~from amino acids~~ from amino acids 320 290 to 410.